Testicular Regression Syndrome

A Clinical and Pathologic Study of 11 Cases

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• ***Context.***—**The vanishing or regressed testis is an entity well known to urologists and pediatric surgeons, affecting approximately 5% of patients with cryptorchidism. However, there is little review and discussion of this entity among pathologists with only 2 of 40 published reviews of testicular regression syndrome (TRS) found in the pathologic literature.**

Objectives.—**To assess recognition of TRS among a subset of pathologists and to determine the applicability of histologic criteria for TRS as published.**

Design.—**An 8-year retrospective review of cases submitted as atrophic or regressed testis was performed. Original diagnosis and diagnosis after review were compared to assess pathologic recognition of TRS. Pathologic assessment included identification of vas deferens, epididymis, dystrophic calcification, hemosiderin, dominant vein, pampiniform plexus–like vessels, and vascularized fibrous nodule formation. At minimum, the presence of a vascularized fibrous nodule (VFN) with calcification or hemosiderin or VFN with cord element(s) was required for diagnosis.**

Setting and Participants.—**Medical records and pathologic specimens of patients undergoing surgery for cryptorchidism or with specimens reviewed at a medium-sized university hospital were analyzed.**

Results.—**The original diagnosis in 3 (23%) of 13 cases was that of TRS. On secondary review, 11 (85%) of 13 cases showed features consistent with TRS. The diagnoses both before and after review showed a concurrence of 23% (3/13 cases). Two (15%) of 13 cases were correctly recognized and diagnosed as TRS at primary review; 1 case originally thought to represent TRS was not confirmed. Pathologic features correlated well with those reported in the literature. Among all 13 cases, the 11 confirmed TRS cases showed VFN in 11 (85%), intranodular calcification in 8 (62%), intranodular hemosiderin in 9 (69%), vas deferens in 9 (69%), epididymal structures in 5 (38%), and a dominant venous structure in 11 (85%). The average size of the VFN was 1.1 cm.**

Conclusion.—**A urologic and pediatric surgical problem, TRS may be unrecognized by many practicing pathologists. In the typical situation in which a blind ending spermatic cord is submitted for tissue analysis, characterization of such cases as consistent with regressed testis is desirable and achievable in a high percentage of cases. Pathologists may play a pivotal role in management of these patients since histologic confirmation of the testis as regressed reassures the surgeon and the family of the correctness of diagnosis and can eliminate the necessity for further intervention.**

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The nonpalpable absent testicle is a problem that confounds urologists and pediatric surgeons alike. This entity, when associated with a blind-ending spermatic cord is referred to as the "vanishing testis syndrome" in the urologic literature[1–3] or "testicular regression syndrome" (TRS) in the pathologic literature,[4] since the presence of spermatic cord structures is evidence of the presence of the testis in early intrauterine life. Up to one half of nonpalpable cryptorchid testes are found on exploration to be "vanished."[2,5,6] Despite the frequency and recognition of the vanished or regressed testis among surgical specialists, there is surprisingly little review and discussion of this entity in the pathologic literature.[7,8]

In the majority of these cases, a fibrous nubbin of tissue is found at the terminus of the spermatic cord. The pathologic findings, where reported,[7–12] show consistent and distinctive features, including discrete fibrosis, dystrophic calcification and hemosiderin deposition. These features, especially when associated with spermatic cord structures, render pathologic recognition of testicular regression accurate.

Failure to discover the gonad at the time of exploration in a patient with spermatic cord duct structures occurs in 1 of 2 situations: (1) the gonad has undergone regression, or (2) the surgeon has not yet localized it. The pathologist may play a pivotal role in the management of these patients. Since 95% of testes are localized at or below the internal inguinal ring,[10] pathologic evaluation of the spermatic cord and confirmation of the testis as regressed on tissues removed at primary inguinal exploration can reassure the surgeon and the patient's family of the proper diagnosis. It can also eliminate the necessity for further surgical intervention or for radiologic evaluation in a majority of cases.

In an effort to determine the recognition of this entity among a small subset of pathologists and to assess the

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utility and applicability of the pathologic features associated in the literature with the tissue diagnosis of testicular regression, case files from a single academic center were reviewed, including 3 cases referred from a separate institution.

PATIENTS AND METHODS

A search of computerized records from the University of Kentucky Medical Center was conducted on all male patients who underwent orchidectomy between mid-1990 and mid-1998 (8 years), focusing on cases in which surgical exploration for cryptorchidism yielded tissue for histologic review. Those cases in which a diagnosis or description of no testicular tissue or seminiferous tubules was made constituted the testicular regression review series, including 3 cases originating from outside of the institution.

Original hematoxylin-eosin–stained microscopic slides from each case were examined. Deeper sections were obtained as necessary for adequacy of evaluation, in a fashion similar to the review and workup of consultation cases. Iron stains were performed in 2 cases in which pigment deposition was not prominent or was borderline in amounts.

Pathologic assessment included identification of vas deferens, epididymis, dystrophic calcification, hemosiderin, dominant vein, and pampiniform plexus–like vessels and presence of a vascularized fibrous nodule (VFN). The original categorization separated fibrosis into discrete and nondiscrete, with or without vascularization, but on review, all cases with significant fibrosis were found to be highly vascularized and at least focally nodular. A dominant vein was required to demonstrate the usual features which would be present in a spermatic vein, including a well-defined intima and media. The pampiniform plexus–like vasculature was required to show congeries of thin-walled ectatic vascular structures in close proximity to one another. The presence of these individual parameters was assessed singly.

Parameters (other than VFN) were also assessed in paired combination as follows: ductal elements (vas and epididymis), vascular elements (vein and pampiniform plexus), and dystrophic change (calcification and hemosiderin pigment). This assessment required at minimum 1 of the 2 associated structures to be present. This was intended to facilitate correlation among the categories of structural elements. The presence of germinal cells, Leydig cells, seminiferous tubules and rete testis was documented in each case.

The gross description of each case was reviewed for identification of a fibrous nodule prospectively. The presence of a nodule was similarly sought within the microscopic description.

The original (primary) diagnosis was compared to the diagnosis after review (the secondary diagnosis). The secondary diagnosis of TRS was determined by presence of the following diagnostic criteria: (1) a vascularized fibrous nodule with calcification and/or hemosiderin or (2) a minimum of a vascularized fibrous nodule with cord element(s) in proximity.

Chart review to assess laterality, type of surgical approach, and operative findings was conducted in all 13 cases.

RESULTS

Of patients meeting criteria for pathologic review, the age range was 9 months to 26 years with a mean of 4.5 years and a median of 2 years. Seven (54%) of the excisions were on the left, and 6 (46%) were on the right.

The original diagnosis in 3 (23%) of 13 cases was that of TRS. On secondary review, 11 (85%) of 13 cases showed features of TRS. The concurrence for primary and secondary diagnosis was also 23% (3/13 cases); however, of 11 cases with secondary findings of TRS, only 2 (18%) had been recognized as such at primary review. (One case originally diagnosed as TRS was subsequently not verified.)

Table 1. Pathologic Parameters for Review Cases Assessed Individually*

Case No.	VFN Size, cm	Dystrophic Change		Cord Structures		Vascular Structures	
		Ca	Hs	Va	E	Ve	P
1	1.4	+	+	+	−	+	−
2	1.0	+	+	+	−	+	+
3	1.0	+	+	+	−	+	+
4	1.2	+	+	+	+	+	+
5	0.8	+	+	+	+	+	+
6	1.1	+	+	+	−	+	−
7	2.0	−	−	+	+	+	+
8	1.1	+	+	−	−	+	−
9	0.9	−	+	−	−	−	+
10	1.2	+	+	−	−	+	−
11	0.7	−	−	+	+	−	+
12	−	−	−	−	−	+	−
13	−	−	−	+	+	+	+

* VFN indicates vascularized fibrous nodule; Ca, calcification; Hs, hemosiderin; Va, vas deferens; E, epididymis; Ve, dominant vein; P, pampiniform plexus; +, presence of parameter; and −, absence of parameter.

Of all 13 cases, 11 (85%) were considered to show features of TRS (cases 1 through 11, Table 1). Two (15%) showed the presence of all 7 parameters (cases 4 and 5, Table 1). Eleven cases (85%) contained a VFN, 8 cases (62%) showed intranodular calcification, 9 cases (69%) showed intranodular hemosiderin, 9 cases (69%) contained vas deferens structures, and 5 cases (38.5%) contained epididymal structures (Figures 1 through 3, a). A dominant venous structure was present in 11 cases (85%). A pampiniform plexus–like structure was noted in 8 (61%) of the cases (Figure 1). The ductal structures were atrophic in appearance in 2 cases. Six of the 8 cases containing calcification and hemosiderin showed giant cell reaction to the deposits. The latter was not a preeminent finding. The degree of calcification and hemosiderin did not correlate with nodule size or presence or absence of other structures. The nodule size ranged from 0.7 to 2.0 cm with a mean of 1.1 cm and a median of 1.1 cm in the 11 cases with VFN.

Nine cases (69%) showed VFN in association with dystrophic change (calcification or hemosiderin) and 2 (15%) showed VFN with an identifiable spermatic cord (both cord ductal and vascular elements present). Six cases (46%) each showed all 4 categories of elements present, including VFN in combination with vas/epididymis, vein/plexus, and calcification/hemosiderin. Three cases (23%) consisted of VFN with dystrophic pigment, 1 of which also contained vascular elements. Two cases (15%) contained VFN along with ductal and vascular structures but lacked dystrophic pigment. Two cases (15%) were without pathologic evidence of TRS as indicated by lack of VFN.

Two of the TRS cases contained Leydig cells on deeper sectioning. Both of these patients were postpubertal. In 1 case, this identification was helpful since no dystrophic change was evident within the nodule. In 2 additional cases, deeper sectioning showed the presence of calcification and/or hemosiderin. Thus, 1 case was diagnostic of TRS that otherwise would not have been so categorized, as only vascularized fibrous nodularity without cord structures was noted originally.

A fibrous nodule or area of discrete fibrosis was noted

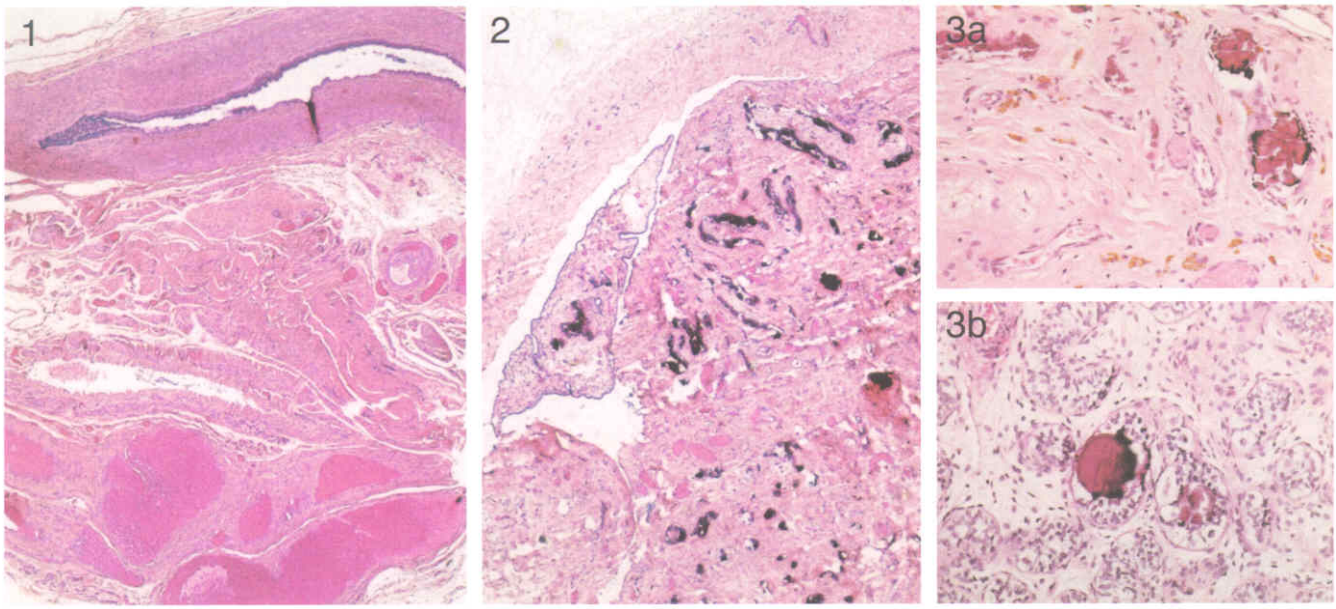

Figure 1. *In most cases, a well-defined spermatic cord with ductal structures and vascular elements was present. In addition to a dominant venous structure, pampiniform plexus–like vascularity was noted (hematoxylin-eosin, original magnification ×80).*

Figure 2. *Characteristic pathologic features of testicular regression syndrome include presence of a discrete highly vascularized fibrous nodule, with dystrophic calcification and hemosiderin deposition. Note that the fibrous focus is in close proximity to the tunica (hematoxylin-eosin, original magnification ×200).*

Figure 3. *Histologically recognizable seminiferous tubules were not identified in atrophic remnants, although serpentine hyalinized structures reminiscent of tubular remnants are noted (a). In b, the presence of seminiferous tubules and germ cells in a cryptorchid testis removed as a presumed atrophic nubbin are seen (hematoxylin-eosin, original magnification ×400).*

on gross description at primary review in 3 cases (23%). In only 1 case (8%) was a fibrous nodule noted in the microscopic description.

At primary review, the number of slides per case ranged from 1 to 12 with an average of 5 slides (4.5) and a mode of 1. These sections represented submission of all tissues received. Deeper sections were used for evaluation in 6 cases. At secondary review, the average number of slides was 6 (6.1) with a mode of 1. Iron stains were performed but were not needed on 2 cases with scant hemosiderin pigment on first review, since deeper sections showed definitive deposits of pigment and calcifications. While cylindrical foci of calcification reminiscent of tubule remnants were noted (Figures 2 and 3, a), neither seminiferous tubules nor germ cells were identifiable in any case. Rete testis was present in 2 cases.

The cryptorchid testis was deemed nonpalpable clinically in 12 cases (92%). In 1 (8%) of these 12, a gonad was thought to be present during examination under anesthesia. Preoperatively nonpalpable testes were as follows: 4 on the right, 6 on the left, and 2 bilateral. A final case was undertaken due to concern over the development of a testicular mass in a patient who previously had undergone left orchidopexy 11 years prior for cryptorchidism. Two surgical approaches were followed: diagnostic laparoscopy followed by same-day open inguinal exploration (3 cases) or inguinal exploration alone (10 cases). The decision to choose laparoscopy as an initial diagnostic tool did not follow a definitive pattern and appeared to be at the discretion of the surgeon. In each laparoscopy, normal appearing vessels were identified entering the contralateral internal inguinal ring. No gonads were present intra-abdominally. The affected side in each case was noted to have small atrophic-appearing vessels entering the internal inguinal ring. In these 3 laparoscopic cases, gonads were present distal to the ring within the inguinal canal.

Of the 13 cases, 10 presumed gonads with blind-ending cords were found below the internal inguinal ring. In 2 cases (15%), blind-ending vessels were described, and in 1 case (8%), no definite testicle or cord as such was identified. Five (38.5%) of the presumed gonads were present in the scrotum. All of the presumed cryptorchid testes found were described as atrophic or as nubbins and were removed, except for 2 cases in which atrophy was noted bilaterally. In the first case, 1 of the 2 remnants was left anchored by orchidopexy in the scrotum. In the second case, testicular tissue was not identified on either side and fibrovascular tissue on 1 side was removed labeled "possible testis." Thus, of 15 presumptively atrophic or absent testes investigated surgically in 13 patients, 13 had tissues removed unilaterally.

Parenthetically, during case accrual as incidental findings, 3 cases showed small fibrous nubbins that had been submitted as atrophic or regressed. Two of them were less than 1 cm and showed atrophy and intratubular dystrophic calcification (Figure 3, b). Each retained the configuration and morphologic features of an intact testis with germ cells present and was diagnosed as cryptorchid testis. Thus, they were not included in the TRS review cases.

COMMENT

The vanishing testis may be better known as testicular regression syndrome in the pathologic literature. Such individuals are genetically male (46, XY), presenting with

Table 2. TRS Study Data Compared With Literature*		
Finding	Range (mean), %	Study, %
Fibrosis	79–100 (91)	85
Calcification	35–93 (61)	61.5
Hemosiderin	30–93 (59)	69
Vas deferens	79–100 (87)	69
Epididymis	24–45 (34)	38.5

* Design in the 6 studies was not exactly comparable. The 1 study similar to the present study requiring absence of testis at exploration differed only in percentage of cases showing calcification and hemosiderin. TRS indicates testicular regression syndrome.

unilateral or bilateral absence of recognizable testis structures and absence of the Müllerian duct system. In actuality there is a spectrum of syndromes characterized as TRS, the exact categorization depending on the stage of fetal or early neonatal life at which testicular function ceased.[4,13,14] Within this range of syndromes, only the vanished testis is associated with late fetal–early neonatal regression.

This condition is not rare. While estimates in the literature range from 4% to 5.5% of the cryptorchid male population,[4,15] the incidence may be higher. One fifth of the 0.7% to 1.0% of males who present with cryptorchidism at age 12 months or older[16,17] are found to have a nonpalpable gonad.[18] Since 40% of this subpopulation are thought to harbor a vanished testis,[8,12,19] as many as 1 male per 1250 may be affected. An 8-year review of cases of nonpalpable testes at Children's Hospital of Philadelphia showed that 41% of 447 boys so affected (181 patients) had an atrophic nubbin or absent testis.[20] Yet it is a condition that is infrequently addressed in the pathology literature. An Internet-based search in late 1998 yielded some 40 articles on the subject since the original report of Abeyaratne et al[1] in 1969 with only 2 of them reported in the pathology literature. Only 6 of the 40 reports[7–12] contain adequate pathologic detail to allow comparison of data or assessment of potential criteria for diagnosis.

One problem may be pathologists' lack of familiarity with this entity. Our study shows a notable lack of recognition of testicular regression syndrome (vanishing testis) among the majority of this subset of pathologists. In only 2 of 11 cases meeting pathologic criteria for TRS was an opinion supportive of that diagnosis rendered, despite the fact that most of these cases were submitted as atrophic or regressed testis. Moreover, 1 of these 2 cases was identified solely based on information regarding the existence of this entity provided by the urologic surgeon.

Eight pathologists were involved in the primary reviews, but only one was aware of the entity of TRS by training, that individual being a urologic pathologist. Additionally, in a case presentation of TRS during a regional continuing medical education program, only 1 of 17 pathologists and none of 11 residents and fellows knew of the entity. This study supports the contention of others[7,8] that TRS is an entity that may be unknown to a considerable number of pathologists.

The potential utility of the pathologic findings reported in association with TRS was also at issue in this study. Six studies[7–12] had sufficient data for comparison of histologic parameters (Table 2). The current study details cases in which the testis was thought pathologically absent while the surgical impression was that of atrophic or degenerative testis. In contrast all but one of the prior pathologic reviews of TRS in the literature were limited to cases selected to show features of TRS supported by surgical findings. Despite differing study designs, these current results compared favorably with prior reports (Table 2).

As noted, 11 cases were characterizable as TRS. The entire constellation of pathologic findings associated with TRS, including findings of a discrete vascularized fibrous focus, cord ductal structures, dystrophic change, and vascularity, was present in almost half of the cases (46%). Nine cases showed a minimum of a vascularized fibrous nodular focus and dystrophic change sufficient to have characterized these cases as consistent with TRS, regardless of clinical findings. In 2 of these 9 cases cord elements were not submitted, and the specimens were fragmented and small (≤2.0 cm). These cases reflect the limitations posed by surgical sampling, but both showed features within areas of fibrous nodularity identical to those of cases submitted along with an intact spermatic cord permitting pathologic recognition. Two additional cases were found to be diagnostic due to association of the discrete vascularized fibrous nodule with cord structures, despite absence of dystrophic calcification or hemosiderin.

Moreover, this study reveals the most constant feature, present in 100% of verified cases, to be discrete vascularized fibrosis, referred to in the surgical literature as a "fibrous nubbin" or "atrophic testis." Fibrosis is reported as the finding most frequently or universally present in TRS in other studies.[7–12] In 2 of the 6 reports delineating pathologic findings, case material was selected predicated on the recognition of a fibrous nubbin.[8,9] If the present study had been limited to those cases in which a discrete nubbin was grossly identified, only 3 cases (23%) would have qualified for review. It may well be that a number of cases of TRS were unrecognized in prior studies.

While the nodular configuration and high degree of vascularity within areas of fibrosis have not been emphasized in studies to date, the discrete vascularized fibrous nodule proved sufficiently distinctive in this review to warrant its recognition as a diagnostic criterion for TRS.

The findings of dystrophic calcification in 61% and hemosiderin pigment in 69% of our cases are well within the range reported within the literature (Table 2). It is desirable that one or both of these dystrophic features be present in cases submitted for diagnosis of TRS, since there is a high degree of association of dystrophic pigment deposition in studies in which the clinicopathologic features have been most closely controlled for correlation of tissue findings with TRS.[8,12] It has been postulated that the ring-like or cylindrical configuration to the calcification supports or suggests origin within preexisting tubules or vessels[8] (Figure 3). Qualified evidence for this assertion appears to be lacking, however.

The surgical literature regarding TRS emphasizes the importance of identification of vasculature supplying and draining the gonad. This is due to the fact that a testis cannot be present in a location absent a gonadal vein and because the vein and pampiniform plexus almost always indicate the location of the testis,[20,21] regardless of the presence of vas deferens and epididymis. This feature has not been emphasized in the pathology literature. This study attempted to assess the predictive nature of the finding of vascular venous structures commensurate with gonadal vein and pampiniform plexus. Unfortunately, the numbers are not sufficient to assess the power of these findings and, of greater importance, evidence is lacking that the domi-

nant venous structure identified microscopically is indeed the gonadal vein. As noted by Turek et al,[10] the surgeon continues to be responsible for the definitive identification of the spermatic vessels.

Of interest, one patient presented with markedly decreased gonadal size 11 years after orchidopexy for cryptorchidism, and this was removed as an atrophic remnant. This patient was the oldest in the series (26 years). While calcification and hemosiderin pigment in the fibrous nodule were lacking, Leydig cells with Reinke crystalloids were present confirming the tissue as regressed testis. This case supports the thesis of vascular compromise as etiologic of TRS, whether due to torsion,[8,15,22,23] kinking of vasculature,[7] direct trauma,[24] or spermatic vascular thrombosis.[11,25] Secondary fibrous replacement of the testicular parenchyma may then lead to the formation of the characteristic vascularized fibrous nodule. This case also provides a link between the microscopic appearance of the VFN of the regressed testes in this study to one verifiable as regressed.

Controversy currently exists regarding excision of vanished remnants.[22,26–28] The relatively low number of cases of TRS in this 8-year review reflects the increasing use of laparoscopy for workup of the nonpalpable testis. With laparoscopic findings of blind-ending or atrophic spermatic vessels at the inguinal ring, TRS is assumed to be present by many of these surgeons, who assert that inguinal exploration with excision of remnants is unnecessary. However, in this study and others,[7,8,20] compelling reasons to remove and submit the testicular remnant for pathologic examination exist. Pathologic confirmation of a vanished, regressed testis reassures parents, patients, and surgeons of the correctness of the diagnosis and eliminates the necessity for additional intervention. This can be accomplished intraoperatively by frozen section in many cases.

Additionally, 2 small cryptorchid testes that were initially submitted as possible regressed testes contained residual germ cells despite areas of atrophy and calcification (Figure 3, b). These viable germ cells would have been retained in situ if recommendations to leave atrophic remnants had been followed.

This study underscores the importance of careful review of tissue sections and evaluation of deeper sections as needed. In 2 cases, foci of calcification and hemosiderin pigment were found in scant amounts on original sections but were sufficiently present on deeper sections to allow for facile identification. In 1 case, review of deeper sections rendered the diagnosis of TRS possible. In 2 additional cases, Leydig cells were identified on deeper sections allowing the tissue specimen to be recognized more definitively as regressed testis. It is stressed, however, that the finding of Leydig cells is limited to pubertal and postpubertal patients, so that diligent search for such elements in the younger patient is apt to be futile.[29]

In summary, TRS is a common urologic and pediatric surgical problem that appears to be unrecognized by many practicing pathologists. In cases of nonpalpable undescended testes, the task of the surgeon is to localize the testis and place it in a scrotal location if possible or to declare it absent. Accordingly, when tissues are submitted for pathologic review, it is not sufficient to report that recognizable testicular tissue or seminiferous tubules are absent, if indeed there is pathologic evidence of regression. In the typical situation in which a blind-ending spermatic cord absent viable testis is submitted for tissue analysis, characterization of such cases as consistent with vanishing or regressed testis is desirable and achievable in a high percentage of cases. This is especially true in those cases in which a fibrous nubbin is identified by the surgeon.

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